

Ketamine for Managing Perioperative Pain in Opioid-dependent Patients with Chronic Pain

A Unique Indication?

IN this issue of ANESTHESIOLOGY, Loftus *et al.*¹ report findings from a study examining the utility of ketamine as an adjunct analgesic in controlling postoperative pain. Is this just another report on the perioperative use of ketamine addressing a question that has already been answered? We know this works, right? Considering that the population under study consisted of patients on long-term opioid therapy for chronic pain, the report may be worth a closer look.

The use of opioids for the control of chronic pain is now commonplace. Opioid prescriptions increased greatly over the past decade, hydrocodone/acetaminophen being the most commonly prescribed drug in the United States for the past several years by a substantial margin.²⁻⁵ Once the province of the pain specialist, long-term opioid prescribing is now in the repertoire of most primary care physicians, and virtually all chronic pain management guidelines endorse the use of opioids at some point in chronic pain treatment algorithms. Few data are readily available to address quantitatively the assertion that an increasing percentage of patients receiving opioids, particularly in large amounts, come to our operating rooms for all types of surgeries, but it seems undeniable.

There is widespread belief among clinicians that patients receiving long-term opioid therapy present significant perioperative management problems. For example, opioid requirements are often greatly increased (on average about three times those of opioid-naïve patients), although prediction of postoperative opioid needs for individual patients remains difficult.⁶⁻⁸ Some have found postoperative pain scores to be worse despite the availability of acute pain management experts.⁸ Perhaps most worrisome, but not well studied, is the notion that the therapeutic index of opioids might be narrowed, making these patients particularly vulnerable to serious side effects or inadequate pain control. Finally, opioid doses tend to be substantially higher, compared with preoperative levels, at the time of discharge from hospital. Dose reduction in this setting can be a complex undertaking. Although the real impact of these challenges remains uncertain, several authors have offered their opinions concerning how patients receiving long-term opioid

therapy should be managed.⁹⁻¹² Most often, the interrelated opioid “maladaptations” of tolerance, opioid-induced hyperalgesia, and physical dependence are cited as the roots of specific management problems.

If we accept that patients receiving long-term opioid therapy are a population of special concern, we might then ask how we would rationally improve their postoperative pain management. Setting aside regional anesthesia, our analgesic trump card, we might opt to use adjunctive analgesics that would both reduce the impact of long-term opioid consumption and contribute to analgesia *via* opioid-independent mechanisms. An ideal drug would reduce opioid tolerance, would attenuate opioid-induced hyperalgesia, and would have proven analgesic properties of its own. Ketamine and perhaps α -2 agonists such as dexmedetomidine may fill the bill. Both ketamine and dexmedetomidine have been advocated as adjuvants in the analgesic management of patients receiving long-term opioid therapy, although there are few data yet to support those recommendations.

The basic and clinical pharmacology of ketamine have been well studied. Although it has many potential sites of action, its *N*-methyl-D-aspartate receptor blocking properties are most frequently discussed. A large body of work in laboratory animals indicates that ketamine can block the development of opioid tolerance and opioid-induced hyperalgesia and reverse both phenomena, at least partly, when already present. Ketamine has specifically been noted to reduce opioid-induced exacerbations of incisional pain in animals.¹³ Curiously, however, studies are mixed as to whether *N*-methyl-D-aspartate receptors strongly support sensitization after incision.¹⁴⁻¹⁶ More broadly, the *N*-methyl-D-aspartate receptor is one of the best studied regulators of pain signaling; these receptors are expressed in various areas in the peripheral and central nervous systems controlling pain sensitization and neural plasticity in many acute and chronic pain states including inflammation, nerve injury, and cancer.

◆ This Editorial View accompanies the following article: Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML: Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. ANESTHESIOLOGY 2010; 113:639-46.

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Many studies have examined ketamine as an adjunctive analgesic in the perioperative period. A recent metaanalysis of 37 trials in more than 2,200 patients indicated that ketamine likely reduces postoperative opioid requirements, at least during the first 24 h.¹⁷ Several studies also reported nominally better pain control, although these observations were not borne out in the combined analysis. The use of ketamine was safe and accompanied by mild side effects, if any. The results of Loftus *et al.*¹ (~30% reduction in morphine consumption over the first 48 h and ~25% reduction in visual analog scale pain score in the postoperative care unit) are similar in magnitude to those previously reported in opioid-naïve patients. No attempt has been made to compare directly responses in opioid-naïve patients *versus* those receiving long-term opioid therapy, leaving unresolved the question of whether ketamine is particularly efficacious in the latter group.

Although the results reported by Loftus *et al.*¹ provide reassurance that the adjuvant analgesic effects of ketamine persevere in the perioperative period in patients receiving long-term opioid therapy, many questions remain. First, the dose and infusion duration of ketamine in this study were similar to those used by others for opioid-naïve patients, but the infusion stopped at the end of surgery. Perhaps enhanced pain control would have been observed if the infusions were continued on the hospital wards. Second, laboratory studies provide the basis to suggest that persons exposed to higher doses of opioids might receive greater benefit from ketamine, a notion supported by an exploratory *post hoc* analysis undertaken by Loftus *et al.*¹ Whether ketamine is of particular benefit for patients receiving high doses of opioids certainly merits future study. Third, comparing particular benefits and potential disadvantages of various adjunct analgesics head-to-head, including ketamine, α -2-adrenergic agonists such as dexmedetomidine, and perhaps gabapentin, would be useful for selecting optimal treatment strategies for this group of patients. Finally, we might wonder whether a reduction in opioid requirements translates into any safety or longer term benefits. Perhaps more aggressive postoperative opioid use is as efficacious and safe as introducing a second medication with its inherent risks and benefits. However, if the use of ketamine widens the therapeutic index for opioids or provides longer term benefits, such as a reduced incidence or severity of more prolonged postsurgical pain states, enthusiasm for ketamine might be higher. Indeed some evidence for reduced chronic (6 week) postoperative pain in the ketamine group was found in the present publication; future studies will be needed to determine whether these effects are sustained.

Loftus *et al.*¹ have provided a valuable first effort in addressing a problem of growing importance. Many of us who have embraced the perioperative use of ketamine for patients receiving long-term opioid therapy may be comforted now that there are some actual data supporting such use. Refining our understanding of ketamine's particular value as an adjunct therapeutic in populations vulnerable to suboptimal

pain control will be necessary and will allow us to target its use toward those patients who would truly benefit.

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